# Exhibit 5

Agri. Puri

# Osteoporosis: The Need and Opportunity for Calcium Fortification[1]

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Osteoporosis is probably as old as humankind. The medical profession has recognized it as a distinct disorder since th end of the last century, but to the public it was for the most part an invisible disease until just a very few years ago. Recently, however, it has been the subject of countless articles in the lay press, and if "osteoporosis" is not exactly a household word today, at least it is now as well recognized as most other medical disorders.

Osteoporosis is not a specific disease. Rather it is a condition that comes about in many different ways. Whatever the mechanism, the net result is a thinning of the bony structures, with a consequent decrease in the mechanical strength of the bone. Thus, a person with osteoporosis suffers various kinds of fractures following even very mild injuries. The disorder itself is entirely silent in most of its varieties and first presents itself when fracture occurs. The two different fracture syndromes appear to be somewhat distinct from one another. In the spine fracture syndrome, the vertebral bodies become crushed, resulting in backache, reduction in height, a bowed back, and inability to get clothes that fit any more. This form of the disorder is overwhelmingly a problem of women and occurs most commonly 10 to 15 years after menopause. A second fracture syndrome involves mainly the long bones, particularly the familiar hip fracture, but also includes shoulder and other extremities and is most common in older individuals, especially those older than 75 or 80. This, too, is principally a disorder of women, with a male to female ratio of approximately 2.5:1. (The actual predominance in women is greater than this figure indicates, because fewer men than women live into the age range at which they are at risk for this kind of fracture.)

Osteoporosis is, thus, predominantly a disorder of the elderly, is responsible for most of the fractures in that age group, and has been estimated, in 1983 dollars, to cost the U.S. more than $3.5 billion annually (1).

## Factors in Osteoporotic Fracture

Many studies indicate that reduced bone mass is the principal factor predisposing individuals to osteoporotic fracture. But there are other important contributory factors, including defective quality of the bony material and architecture and a propensity to fall (Fig. 1). In a strict sense, the term, osteoporosis, relates only to the condition of decreased bone mass, but because mass is of little interest apart from the fracture event, any discussion of osteoporosis must take into consideration the entire set of fracture-related risk factors. Furthermore, these factors interact in important and interesting ways. For instance, as bone mass declines, the bony structures deform more under loading. As in other solid materials, this can lead to an accumulation of microscopic cracks. Normally, the bone remodeling process repairs these cracks by replacing the damaged material with fresh, new bone. In some cases of osteoporosis, the repair process cannot keep up with the strain-related microscopic damage, and materials fatigue develops and exaggerates the fragility due first to decreased mass. The importance of this factor is highlighted by the fact that certain forms of calcium supplements suppress the remodeling process more than others (2). Much more needs to be learned about this kind of therapy-induced remodeling suppression, but it is nevertheless easy to see how this component of fracturability is a potentially important consideration in planning food fortification.

The full explanation for why osteoporosis is more common in women than in men is not fully understood, but several reasons are known to contribute to the difference: 1) Women have smaller skeletons than men, and skeletal size is, in the last analysis, probably the single most important factor in determining fragility. 2) Women undergo accelerated bone loss at menopause. This is entirely due to estrogen loss and is indefinitely preventable with estrogen replacement. 3) Women tend to be less physically active than men and to do less strenuous work. Mechanical loading of the skeleton is a major factor in determining and maintaining skeletal size. 4) Women consume substantially less calcium than do men. This last difference, the only clearly nutritional one, needs to be seen in the context of all the others. If calcium intake is limiting for some women, correcting that limitation would be expected to be helpful but doing so will not, *ipso facto*, obliterate the other differences. Osteoporosis is a multifactorial problem and it may be expecting too much to hope to solve it with any single strategy.

## Osteoporosis and Calcium Nutrition

So far as is now known, only the factor of reduced bone mass (Fig. 1) is related to calcium nutrition. We have recognized in many animal species for more than 80 years that if calcium intake is reduced below need, osteoporosis will develop, and that this osteoporosis, in turn, can be largely reversed by replacing the missing nutrient. The same is probably true with respect to human nutrition, but controversy continues over what the human requirement really is. The recommended dietary allow-

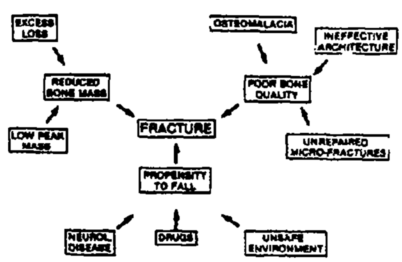


**Fig. 1. Three principal risk factors in osteoporotic fracture. For each factor, some of its more important components are also depicted.**

[1]Adapted from a presentation as part of the AACC short course "Who Says Nutrition Doesn't Sell?" held Sept. 20, 1985, in Orlando, FL.





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ance for nonpregnant, nonlactating adult females has been set at 800 mg/day for many years, but few experts are very comfortable with this figure. The recent NIH Consensus Conference on Osteoporosis recommended that the perimenopausal woman increase her intake to 1,000 mg if she is estrogen-replete and to 1,500 mg if estrogen-deprived (1). This recommendation was based on the observation that middle-aged women cannot achieve calcium balance at intakes of less than 1,000 mg (3); on observations that calcium absorption efficiency declines with age (4); and on the fact that estrogen deficiency leads to decreased calcium absorption and decreased retention of absorbed calcium (5).

Evidence from the field regarding the actual efficacy of high calcium intakes remains mixed, probably because the issue is complicated by genetic, occupational, and other differences across populations. One notable study that seemed to avoid such problems reported findings in two Yugoslav regions that differed from one another predominantly in the fact that the occupants of one region herded goats (and therefore had access to goat's milk and cheese in the daily diet), whereas occupants of the other did not (6). As a result, the calcium intake of the goat-herding region at every age was approximately twice that of the other region. Bone mass was consistently higher at all ages, in both men and women, in the high calcium intake region, and what is certainly of greater significance, the prevalence of hip fractures in women in the high calcium intake region was approximately one-fourth that of women in the low calcium intake region. (Actual intakes in the high calcium region were in the range recommended by the NIH Consensus Conference.)

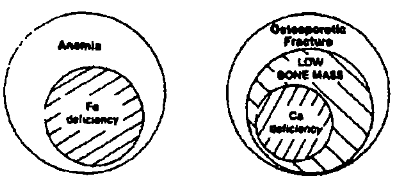


**Fig. 2. Relation of calcium and iron intakes to osteoporotic fracture and anemia, respectively.**

Because osteoporosis is not a specific disease, but a condition which comes about as a result of many different mechanisms, one would expect that calcium deficiency would be a factor in only some osteoporotics and that ensuring an adequate calcium intake would protect against *only some* osteoporotic fractures. Even in the same individual, calcium intake is probably more important for certain bony regions than for others. The reasons are not at all understood, but impressive evidence indicates that high calcium intake protects against bone loss and fracture in some parts of the skeleton but not in others (7). Thus, in the Yugoslav study, despite striking protection against hip fracture, wrist fracture prevalence was the same for both regions.

A useful parallel may be drawn between the relation of calcium and osteoporosis on the one hand and of iron and anemia on the other (Fig. 2). Assuring an adequate iron intake will protect some women against iron deficiency anemia caused by an inadequate intake but will obviously not protect against all types of anemia, not even against all forms of iron deficiency anemia, some of which may be due to blood loss in excess of what can be replaced from any reasonable intake. Thus, not all osteoporotic fractures are due simply to the decrease in bone mass, and not all decrease in bone mass is due simply to calcium deficiency (Fig. 2). Assuring an adequate calcium intake for all of the population would not entirely solve even the calcium deficiency problem, because some members of the population absorb so poorly that even a generous intake would not be enough. Misunderstanding and confusion about this topic is great, and the potential benefit that might accrue from assuring an adequate calcium intake in our population might be lost by expecting calcium to do more than it possibly could. We would not make that mistake about iron fortification today, but our current understanding of osteoporosis is probably comparable to our understanding of anemia 60 or 80 years ago.

## Status of Calcium Nutrition

Nutrient requirements and recommended dietary allowances are one thing, but actual intakes are another. The HANES studies of the U.S. Public Health Service have shown clearly that the typical adult female in the United States consumes less than 600 mg of calcium on a typical day, and by the time she reaches the age of menopause, less than 500 mg (8,9). This is a drastic departure from the recommended dietary allowances (Fig. 3). Furthermore, approximately one-fourth of all females ingest less than 300 mg on a typical day. Perhaps of even greater significance is the 10% drop in median calcium intake in adolescents from the early 1970s to the late 1970s.

It is instructive to compare such intake performance with what might be considered a more natural calcium intake. Recent studies of hunter-gatherer tribes indicate that paleolithic humans probably were adapted to a calcium intake of more than 1,500 mg/day, virtually all of which was derived from vegetable sources (10). The principal source of calcium in a civilized, Western diet is dairy products, but this is partly because we have decreased both the variety of foods that we ingest and our total food intake at the same time. Many foods that were perhaps more commonly eaten in the past than they are today, are good sources of calcium (Fig. 4); dairy products are not, by any means, the only rich source of calcium in the food chain.

Nevertheless, the U.S. female population probably will not change its eating habits enough to result in a substantial increase in calcium intake from such natural sources. Furthermore, because total food intake declines with age and calcium absorption efficiency deteriorates, an adequate calcium intake for the

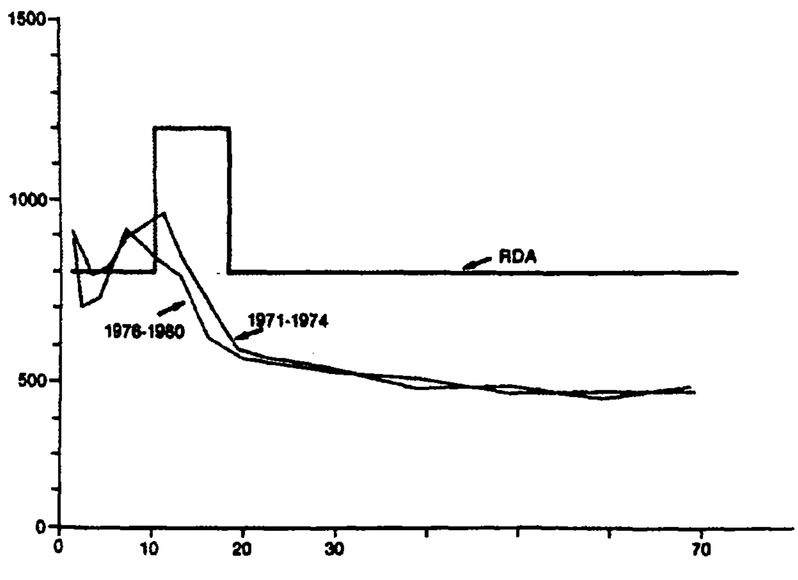


**Fig. 3. Median calcium intake for U.S. females at various ages for HANES I (1971–1974) and HANES II (1976–1980) in relation to the current RDA (8,9). Note the deterioration in intake during the adolescent years between the two studies.**





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U.S. population cannot be assured from dietary sources alone. This inevitably leads to the conclusion that we must look either to the use of calcium supplements or to food fortification.

There are many practical problems with calcium supplements. They require a high level of commitment and motivation, which must be sustained over a long period of time. They can easily create imbalances of other nutrients (e.g., zinc and iron), and what may be more important, their use breeds the undesirable notion that one can be healthy only by taking pills. Advertising, packaging, distribution, and other such costs probably also make supplements the most expensive way of producing the desired effect.

In the past, whenever we have encountered a comparable situation, one in which we have found ourselves unable to get an adequate quantity of a certain nutrient in the food chain, we have moved toward some appropriate fortification policy. We have done this by adding fluoride to the water supply, iodine to table salt, vitamin A to low-fat milks, and various enrichments to white bread flour. The time has come to do this with calcium as well.

Several attractive options are available, including standardizing milk at a higher solids content (as California has done for several years), adding nonfat dry milk solids or freeze-dried whey products to bread and flour, fortifying breakfast cereals with whey products, and adding small amounts of bone meal to various forms of processed meats, canned soups, stews, spaghetti sauces, and other canned foods. Now being test marketed is at least one breakfast food that uses calcium phosphate and whey concentrates to supplement the calcium content of the cereal grain and which, with a one-half cup of milk, provides the full recommended dietary allowance (800 mg) in a single serving. Soft drink manufacturers are also interested in producing a calcium-fortified beverage. This is probably a prudent move in view of the current addiction of young women to soft drinks.

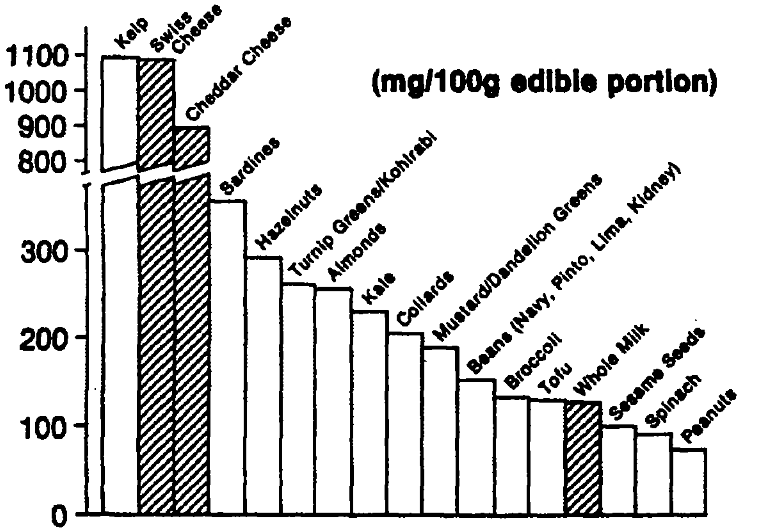


**Fig. 4. Calcium contents of various foods, most of which are available in a typical Western diet. Dairy products are shaded for comparison purposes.**

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He received undergraduate and medical degrees at Creighton and internship and residency training in internal medicine at St. Louis City Hospital in St. Louis, MO. Heaney served research fellowships at the Oklahoma Medical Research Foundation in Oklahoma City, OK, and at the National Institutes of Health in Bethesda, MD. He has held faculty appointments at the University of Oklahoma, at George Washington University, and at Creighton, where he served as chairman of the Department of Internal Medicine from 1961 until 1969 and as vice-president for health sciences from 1971 until 1984.

Heaney actively participates in several research-related professional societies and serves as a consultant for a variety of scientific, academic, civic, and church-related organizations. He has also served as chairman of the board of the Association of Academic Health Centers and on the editorial boards of several scientific publications, and is a trustee of Loyola University, Chicago, IL.

He is principal investigator for one of the major government-sponsored research projects dealing with human osteoporosis and is an internationally recognized expert and lecturer in this field. He has published more than 100 original papers, chapters, monographs, and reviews.

## Safety

Questions of safety inevitably and appropriately arise whenever one considers increasing intake of calcium, or any nutrient, across an entire population. Renal stone disease is the principal concern raised in this regard. There is much misunderstanding about this problem. Kidney stones are not so much caused by calcium in the diet as by failure of the kidneys to produce a product that keeps its components in solution. (Urine is normally supersaturated with respect to calcium and other salts, even on low calcium intakes, and we would all form stones, most of the time, if the kidneys did not secrete various crystal inhibitors that prevent stone formation.) A small portion of the population absorb dietary calcium with unusual efficiency, and these persons excrete the absorbed load through the kidneys. If they happen also to be prone to renal stones, the extra absorbed calcium aggravates their problem. But it does not cause it. The problem of these few persons (who may be thought of as calcium-sensitive) should not prevent reasonable attempts to improve calcium nutrition in the vast majority of the population. The best current estimates indicate that intakes of up to 2.5 g/day (and probably much higher) are quite safe (11). It hardly seems unreasonable to increase intakes from their current low values at least part way toward levels known to be ingested routinely by healthy hunter-gatherer tribes (10) and by the typical adolescent boy (8,9).



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## Conclusion

Not all of the osteoporosis problem is calcium related, but the part that is can be substantially eliminated by assuring an increase in the calcium intake of the U.S. population, particularly white females. Once thought to be necessary primarily only for growth, calcium is now recognized as an essential nutrient throughout life. Most U.S. women consume far less calcium they they ought, and most of them probably will not alter their intakes sufficiently to give them as much calcium as they require. This need seems to provide a natural opportunity for food fortification and, given the current level of popular interest in osteoporosis and in assuring adequate calcium intake, a natural marketing opportunity as well.

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